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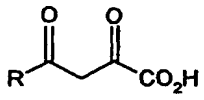

(A)

(57) Abstract

Diketoacids of Formula (A) are useful as inhibitors of viral polymerases. In particular hepatitis C virus RNA dependent RNA polymerase (HCV RdRp), hepatitis B virus polymerase (HBV pol) and reverse transcriptase of human immunodeficiency virus (HIV RT). The group R may be broadly chosen and is an organic moiety which contains 2 to 24 carbon atoms and includes an optionally cyclic or heterocyclic group in which the atom directly bonded to the adjacent carbonyl in the diketoacid is part of the ring structure.

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DIKETOACID-DERIVATIVES AS INHIBITORS OF POLYMERASES

Technical Field

The present invention relates to compounds useful as enzyme inhibitors, in particular as inhibitors of enzymes involved in the transfer of phosphoryl groups and, especially as inhibitors of polymerases. The invention further relates to pharmaceutical compositions containing such compounds, and to their use in the treatment of viral infections.

Polymerases are the enzymes which catalyse the formation of phosphodiester bonds in RNA and DNA. They play an essential role in viral replication and, therefore, are an important target in the fight against viral diseases such as human immunodeficiency virus (HIV), hepatitis, and poliomyelitis.

Background Art

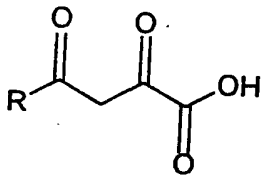
US 5 475 109 describes dioxobutanoic acids substituted with piperidine or similar N-substituted saturated cycloalkyls as inhibitors of the cap-dependent endonuclease of influenza virus.

Disclosure of the Invention

The present inventors have discovered that a range of

diketoacids have utility as enzyme inhibitors and, in particular, as polymerase inhibitors and more particularly as inhibitors of hepatitis C NS5 RNA-dependent RNA polymerase, HBV DNA-dependent RNA polymerase and HIV DNA- dependent DNA polymerase. Their investigations indicate that these compounds may act by interfering with the binding of phosporyl groups at the active site of the enzyme and may, therefore, have broad application in inhibiting enzymes involved in the transfer of phosphoryl groups.

According to a first aspect of the present invention there is provided a compound of formula A shown below. This compound is suitable for therapeutic use, for instance as an enzyme inhibitor.



FORMULA A

Optionally, the compound may be in the form of a pharmaceutically acceptable salt or ester, which can be hydrolysed in vivo to the corresponding diketoacid.

In formula A, the group R is an organic moiety which contains from 2 to 24, preferably 4 to 20, most preferably 6 to 17 carbon atoms in total. R includes an optionally substituted cyclic or heterocyclic group in which the atom directly bonded to the adjacent carbonyl in the diketoacid is part of the ring structure. Preferably, this atom is a carbon atom.

The ring which is thus bonded to the carbonyl group is preferably a 3 to 8 membered ring, particularly a 4 to 6 membered ring.

Thus, for example, R may be selected from:

(i) optionally substituted aromatic groups, especially those including six membered rings, such as phenyl and naphthyl;

(ii) optionally substituted heteroaryl groups especially those including five and six membered rings such as thiophene, pyrrole, furan, imidazole, pyridyl, pyrimidyl, and pyridazyl; the heteroaryl ring may, optionally be fused to another ring;

(iii) optionally substituted cycloalkyl groups,

especially those including five or six membered rings such as cyclopentyl, cyclohexyl and adamantyl;

(iv) optionally substituted cycloalkenyl groups, especially those including five or six numbered rings such as cyclohexenyl, cyclopentenyl;

(v) optionally substituted cyclic heteroalkyl groups, especially those including five or six numbered rings such as piperidyl, pyrrolidyl, tetrahydrofuranyl, and tetrahydropyranyl; in this class 4- piperidyl rings substituted with an aryl group at carbon 4 and on acyl or sulfonyl substituent at N1 are preferred.

In the case of optional substitution, one or more substituents may be present and a wide variety of substituents are possible. Preferred optional substituents for all compounds of the present invention are set out in the following list:

(a) -OH;

(b) -SH;

(c) - halogen, such as fluorine, chlorine or bromine,

(d) - CO_2H;

(e) - CN;

(f) - NO_2 ;

(g) - NR_1R_2 wherein each of R_1 and R_2 is selected from H and lower alkyl groups having 1 to 6 carbon atoms; or R_1 and R_2 together form a ring including 4 to 6 carbon atoms;

(h) - $SO_2NR_1R_2$ where R_1 and R_2 are as defined above;

(i) $-CONH_2$, - $NHCO_2H$, or -NHCOCOOH;

(j) an alkyl (or alkenyl or alkynyl group) group having 1 to 12 (2 to 12) carbon atoms, preferably 1 to 7 (2 to 7) carbon atoms optionally substituted by any one or more of the groups (a) - (i) above and/or optionally interrupted by a group selected from -O-, -S-, $-NR_3-$,

$-CO_2-$, -OCO-, $-CONR_3-$, $-NR_3CONR_3-$, $-SO_2-$, $-NR_3SO_2-$, and $-SO_2NR_3-$; where each R_3 independently is H or lower alkyl of 1 to 6 carbon atoms;

(k) an aryl or heteroaryl group having 2 to 10 carbon atoms optionally substituted with any one or more of groups (a) to (j) above;

(l) an aralkyl or heteroaralkyl group having 3 to 16 carbon atoms optionally substituted with any one or more of groups (a) - (j) above and/or in which the

alkyl part of the group is optionally interrupted by a group selected from

$-O-$, $-S-$, $-NR_3-$, $-\overset{O}{\overset{\|}{C}}-$, $-CO_2-$, $-OCO-$, $-CONR_3-$, $-NR_3CONR_3-$, $-SO_2-$, $-NR_3SO_2-$, and $-SO_2NR_3-$; where R_3 is as defined above;

(m) $-\overset{O}{\overset{\|}{C}}-R_4$ where R_4 is an alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, or heteroaralkyl group as such groups are defined above at (j), (k) and (l);

(n) $-\overset{O}{\overset{\|}{C}}-O-R_4$ or $-O-\overset{O}{\overset{\|}{C}}-R_4$ where R_4 is as defined above;

(o) $-OR_4$ where R_4 is as defined above;

(p) $-CNHR_4$, $-NH-\overset{O}{\overset{\|}{C}}-R_4$ or $-NH-\overset{O}{\overset{\|}{C}}-NHR_4$ where R_4 is as defined above;

(q) $-SO_2R_4$ where R_4 is as defined above;

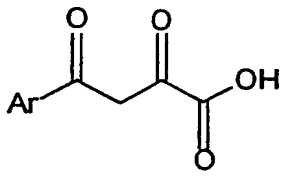
(r) $-NHR_4$ or $-N(R_4)_2$ where R_4 is as defined above;

(s) $-NHSO_2R_4$ or $-SO_2NHR_4$, where R_4 is as defined above;

(t) $-SR_4$

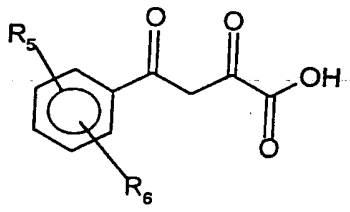
and each of optional substituents (j) to (t) above may optionally itself be substituted by one or more groups selected from (j) to (t).

A preferred class of compounds of formula A is represented by formula E:

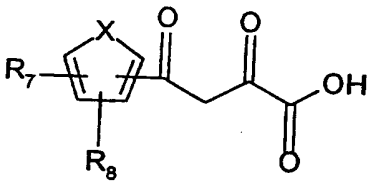


FORMULA E

in which Ar is an optionally substituted aryl or heteroaryl group. Optional substituents may be selected from the list of preferred substituents set out above. Within this class of preferred compounds two especially preferred groups are set out below (formulas F and G)



FORMULA F



FORMULA G

R_5, R_6, R_7 and R_8 are, independently H or are selected from the optional substituents listed above and R_7 and R_8 taken together may form a 4 to 7, preferably 5 or 6 membered ring; and X is O, S, NH, or NR_4 where R_4 is as defined above.

In compounds of formula F, (which are optionally substituted phenyl diketoacids) ortho, meta and para

substitution are possible.

In general, it is preferred that there is a single substituent, preferably at the position which is ortho- or meta- to the diketoacid group. Substitution at the meta-position is especially preferred. Where two substituents are present, then preferably the phenyldiketoacid is 2,5-substituted; 3,5-substitution is also possible, as is 2,4-substitution provided, in the latter case, that the substituent at the 4-position is relatively small (e.g. methyl). Disubstitution at the 2,3- and 2,6-positions is, in general, not preferred.

Preferred substituents, especially at the ortho and meta positions, are ether groups of formula (o) above (i.e. $-OR_4$), hydroxyl, and $-NHSO_2R_4$. It is generally preferred that no more than one substituent be $-OR_4$ and/or $-NHSO_2R_4$.

Preferred examples of $-OR_4$ groups which may be found at the ortho and meta positions and particularly at the meta position include:

$-OCH_2Ar$ or, less preferably $-O(CH_2)_2Ar$ where Ar is an optionally substituted aryl or heteroaryl group and is particularly preferably an optionally substituted phenyl

group. Examples of preferred substituents on the aryl group, and especially on the phenyl ring include halogens, especially fluorine and chlorine, and electron-withdrawing groups such as -CN, $-CO_2H$, and $-CF_3$ as well as ether and aryl groups;

$-O-(CH_2)_3-CN$; and

$-O-(CH_2)_3-C\equiv CH$.

Preferred sulfonamide groups which may be found at the ortho- and meta- positions, particularly at the meta-position are those of formula:

$-NH-SO_2-Ar$, where Ar is an optionally substituted aryl or heteroaryl group, preferably an optionally substituted phenyl group. Preferred optional substituents for the aryl, preferably phenyl group, include: -CN; halogens, especially chlorine and fluorine, $-CF_3$, lower (C_{1-6}) alkyl (especially methyl), hydroxy-, ether, and $-NO_2$ groups.

For both the $-OCH_2Ar$ and $-NHSO_2Ar$ substituted compounds, another preferred example of Ar is naphthyl.

Other preferred substituents at the ortho and meta positions are lower (eg C_{1-6}) alkyl groups, especially C_{1-4} alkyl, such as methyl and ethyl, but in particular methyl, aralkyl groups, especially phenylmethyl groups,

optionally substituted in the phenyl ring, especially by a halogen, and nitrogen-containing substituents such as primary, secondary or tertiary amine groups, optionally in protonated form, amide, urethane, or urea groups in each of which examples there is a nitrogen atom bonded to the phenyl ring.

One particularly preferred sub class of compounds of formula F is those in which each of R_5 and R_6 is selected from H, HO-, R_4O-, and $-NHSO_2R_4$ provided that no more than one of R_5 and R_6 is R_4O- or $-NHSO_2R_4$.

In compounds of formula G the diketoacid group may be at the 2- or 3- position of the ring. In many cases substitution at the 2-position is preferred.

Preferred examples of compounds of formula G are those in which the five membered aromatic ring,

is a pyrrole or thiophene ring. In the case of the pyrrole-substituted diketoacids, the groups R_7 and R_8 may both be hydrogen and in many cases that is preferred. If R_7 and R_8 correspond to substituent groups, then these may

be at any of the positions not already occupied by the diketoacid group. Examples of possible substituents include alkyl (especially methyl), halogen, and aralkyl (especially benzyl) groups.

One embodiment of pyrrole substituted diketoacid is that in which the diketoacid group is at the 2- position of the ring and where the only other substituent in the ring is on the nitrogen atom. In this case, preferred examples of the substituent R_4 present on the nitrogen atom, include alkyl, aryl or aralkyl groups, particularly aralkyl (such as benzyl) groups. Where an aryl or aralkyl group is present these are preferably substituted with halogen atoms, such as fluorine or chlorine, or by cyano-groups.

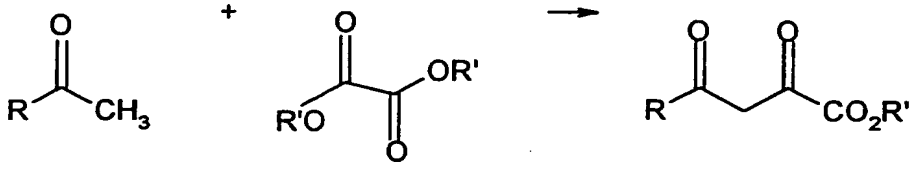
In the case of the thiophene-substituted diketoacids a wide range of substituents R_7 and R_8 may be employed in various positions as will be evident from the tables infra. Preferred thiophenes have an aralkyl (such as optionally substituted benzyl) or aryl (such as optionally substituted phenyl) substituent, e.g. at the 5-position of the thiophene ring.

Compounds containing furanyl rings may also be useful, especially for inhibiting HIV reverse transcriptase.

Preferred substituents are optionally substituted aryl groups (especially optionally substituted phenyl). Substitution is preferably at the 5-position of the ring.

The formulae of numerous preferred specific compounds of the present invention are presented later below.

The compounds of the present invention having formula A may be prepared by a process which comprises reaction of a compound of formula B with a dialkyloxalate of formula C followed by hydrolysis of the resulting diketo-ester of formula D:



FORMULA B FORMULA C FORMULA D

where R ' is an alkyl group, typically having 1-6 carbon atoms. In the case where the target molecule is a pharmaceutically acceptable ester of the compound of formula A then R ' in formula C may be selected accordingly, and the step of hydrolysing the compound of formula D omitted, since in vivo hydrolysis can render

the compounds active.

Preferred enzymes for inhibition by the compounds of the invention are those involved in phosphate transfer, in particular polymerases such as DNA polymerases, and RNA polymerases both of which may be either RNA dependent or DNA dependant. Compounds of the invention may particularly preferably be employed in the inhibition of viral enzymes. Examples of viral enzymes include RNA - dependent RNA polymerase and reverse transcriptases.

The compounds of the invention may be used as inhibitors of plant or animal (including human) viruses.

The viruses may be RNA viruses, which may, for example, be positive single stranded viruses of which polio virus, hepatitis C virus and encephalomyocarditis are examples, negative single stranded viruses such as orthomyxoviruses, and paramyxoviruses, and retroviruses of which HIV is a prominent example. Alternatively, the viruses may be DNA viruses, especially double stranded DNA viruses such as hepatitis B virus. In particular, compounds of the present invention may inhibit one or more of the following enzymes: hepatitis C virus RNA dependent RNA polymerase (HCV RdRp), hepatitis B virus polymerase (HBV pol) and reverse transcriptase of human

immunodeficiency virus (HIV RT).

Especially preferred compounds of the invention will be suitable for use as HCV RdRp inhibitors.

Other classes of enzyme involved in phosphate transfer which may be susceptible to inhibition by compounds of the present invention include phosphatases, Rnases, integrases and ribozymes.

According to a further aspect of the invention there is provided the non-therapeutic use of compound of formula A or suitable salt or ester as an enzyme inhibitor, especially as an inhibitor of polymerases, especially viral polymerases. For instance, compounds of the invention may be of utility in agriculture and horticulture for treating plants infected with or susceptible to plant virus.

According to a further aspect of the invention there is provided the use of a compound of formula A or of a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for treatment of a viral illness in a human or animal. For instance, the medicament may be used to treat viral illness by inhibiting one or more viral polymerase. Preferably the

medicament is for treatment of hepatitis, such as hepatitis B or C, particularly hepatitis C, and human immunodeficiency virus.

A still further aspect of the invention provides a pharmaceutical composition comprising a compound of formula A, or a pharmaceutically acceptable salt or ester thereof and a pharmaceutically acceptable excipient, diluent or carrier. The composition may be in any suitable form, depending on the intended method of administration. It may for example be in the form of a tablet, capsule or liquid for oral administration, or of a solution or suspension for administration parenterally.

The pharmaceutical compositions optionally also include one or more other agents for the treatment of viral infections such as an antiviral agent, or an immunomodulatory agent such as α-, β-, or γ- interferon.

A still further aspect of the invention provides a method of inhibiting an enzyme, especially a viral polymerase and/or of treating or preventing a viral illness, the method involving administering to a human or animal (preferably mammalian) subject suffering from the condition a therapeutically or prophylactically effective amount of the pharmaceutical composition described above

or of a compound of formula A or salt or ester thereof. "Effective amount" means an amount sufficient to cause a benefit to the subject or at least to cause a change in the subject's condition.

The dosage rate at which the compound, salt or ester is administered will depend on the nature of the subject, the nature and severity of the condition, the administration method used, etc. Appropriate values are selectable by routine testing. The compound, salt or ester may be administered alone or in combination with other treatments, either simultaneously or sequentially. For instance, it may be administered in combination with effective amounts of antiviral agents, immunomodulators, anti-infectives, or vaccines known to those of ordinary skill in the art. It may be administered by any suitable route, including orally, intravenously, cutaneously, subcutaneously, etc. It may be administered directly to a suitable site or in a manner in which it targets a particular site, such as a certain type of cell. Suitable targeting methods are already known.

A further aspect of the invention provides a method of preparation of a pharmaceutical composition, involving admixing one or more compound of formula A or salt or ester thereof with one or more pharmaceutically

acceptable adjuvants, diluents or carriers and/or with one or more other therapeutically or prophylactically active agents.

Modes for Carrying Out the Invention

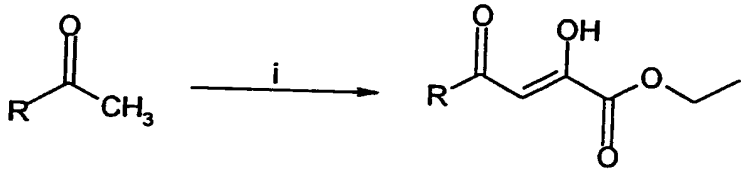
Embodiments of the invention are described below by the way of example only.

EXAMPLES

(1) Synthesis

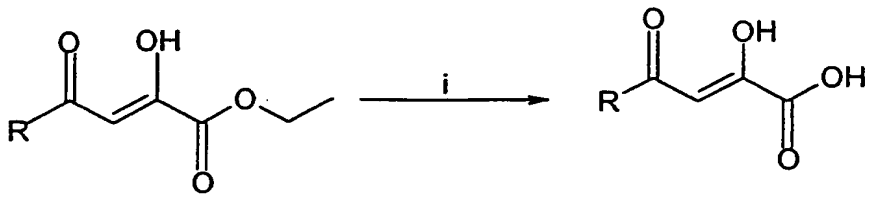
The synthesis of the 2,4-dioxobutanoic acids consists of a Claisen condensation reaction between a methyl ketone substrate and diethyl oxalate in the presence of sodium ethoxide in tetrahydrofuran (Scheme 1A) and the subsequent hydrolysis of the ethyl ester with sodium hydroxide in methanol (Scheme 1B)

Scheme 1A



Reagents: (i) diethyl oxalate/NaOEt in THF

Scheme 1B



Reagents: (i) 5eg. NaOH/MeOH

Exemplary procedure for the synthesis of the 2, 4 -dioxobutanoate ethyl esters

(Scheme 1A)

In a 50 ml round bottom flask with a stirring bar and under an inert atmosphere, the methyl ketone compound (1.0 mmole) in 10 ml of dry tetrahydrofuran (THF) is reacted with 2 equivalents of diethyl oxalate and 2 equivalents of sodium ethoxide (NaOEt) at ambient temperature for 3 hours. When reaction is completed, the reaction mixture is poured into a 1N aqueous hydrochloric acid (HCl) and extracted with ethyl acetate (EtOAc). The organic phase is separated, washed first with water and then with brine. The organic layer is dried over sodium sulfate (Na2SO4), filtered and solvent is removed in vacuo leaving the desired dioxobutanoate ethyl ester in quantitative yield.

Exemplary procedure for hydrolysis of the ethyl ester

(Scheme 1B)

In a 50 ml round bottom flask with a stirring bar, the 2,4-dioxobutanoate ethyl ester compound (1.0 mmole) in 10 ml of methanol (MeOH) is reacted with 5 equivalents of sodium hydroxide (NaOH) at ambient temperature for 2 hours.

The methanol is removed in vacuo. The aqueous residue is washed with diethyl ether (Et20). The aqueous fraction is acidified by addition of 1N aqueous hydrochloric acid solution (HCl) and the milky mixture is extracted with two portions of ethyl acetate (EtOAc). The combined organic fractions are washed with brine. The organic layer is dried over sodium sulfate (Na2SO4), filtered and solvent is removed in vacuo leaving the desired dioxobutanoic acid product.

Using this or analogous methods, compounds were produced as set out in the following Tables, which are categorised according to their "R" group.

The Tables include IC_{50} data and the methods for assay are explained after the Tables.

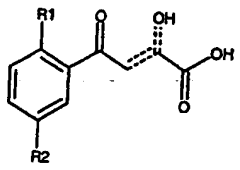
Notes to Table: NA = not active as an inhibitor at concentrations up to that stated.

ND = not done.

In the tables, where nitrogen atoms appear to be divalent, the presence of a hydrogen atom is implied.

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



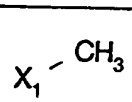
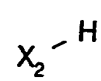
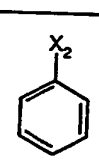
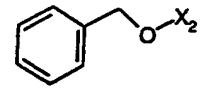
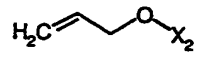
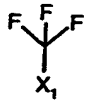
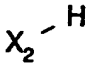
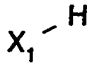
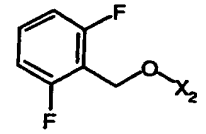
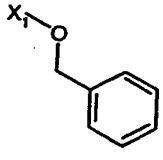
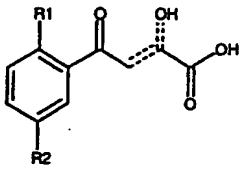
Ex. No.	R1	R2	IC 50 (μM)
1			5.6
2			3
3			27.9
4			8
5			17
6			18
7			2.92
8			44

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



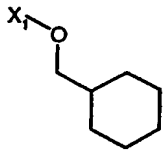
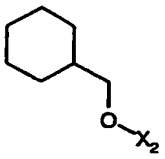
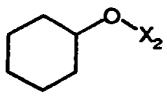
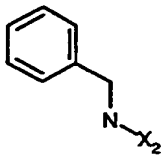
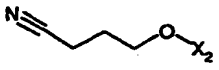
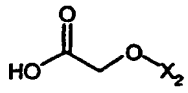
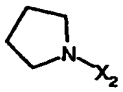
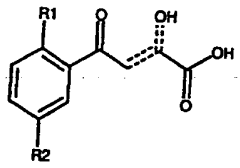
Ex. No.	R1	R2	IC 50 (μM)
9			51
10			20
11			7.08
12			16.7
13			2.6
14			26
15			83.5

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



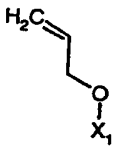
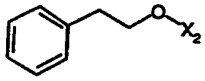
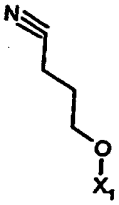
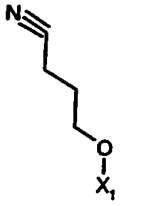
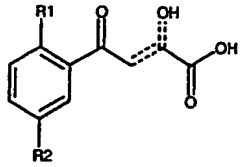
Ex. No.	R1	R2	IC 50 (μM)
16			4.3
17			11.6
18			2.2
19			11.9
20			0.38
21			0.955

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



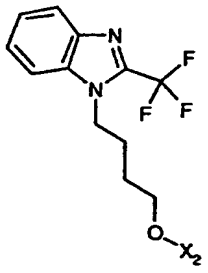
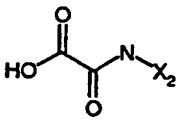
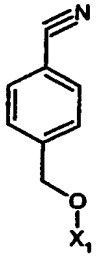
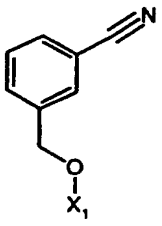
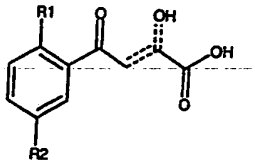
Ex. No.	R1	R2	IC 50 (μM)
22			19
23			0.94
24			19
25			28
26			26

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



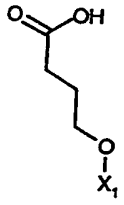
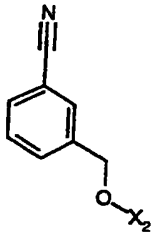
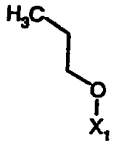
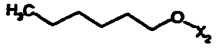
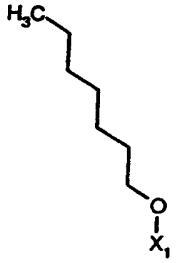
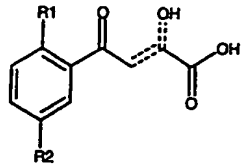
Ex. No.	R1	R2	IC 50 (μM)
27			2.84
28			6.2
29			3.9
30			15
31			18

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



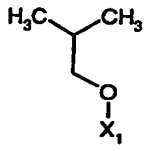
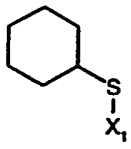
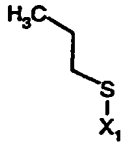
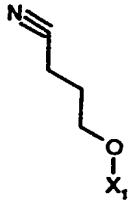
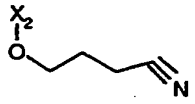
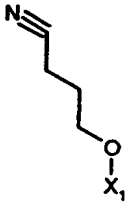
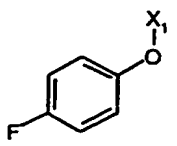
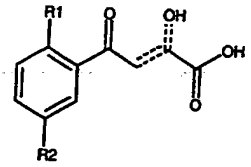
Ex. No.	R1	R2	IC 50 (μM)
32			6.1
33			18.2
34			9.6
35			6.1
36			1.6
37			18

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



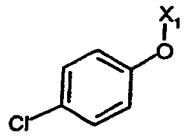
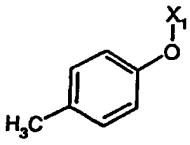
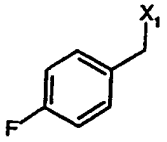
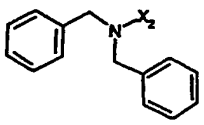
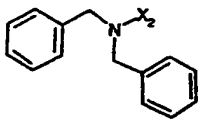
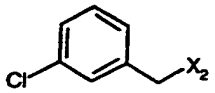
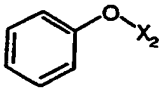
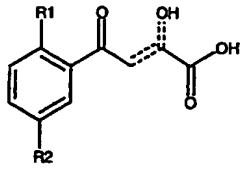
Ex. No.	R1	R2	IC 50 (μM)
38			16
39			22
40			8.3
41			28.9
42			16.6
43			20
44			18.5

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



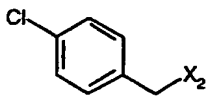
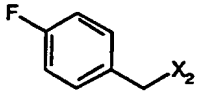
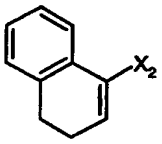
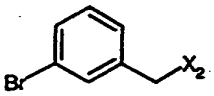
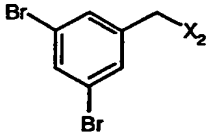
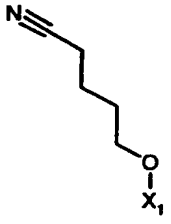
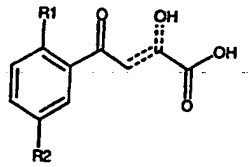
Ex. No.	R1	R2	IC 50 (μM)
45			12.9
46			30.1
47			20.7
48			22
49			32
50			7.8

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



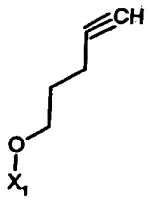
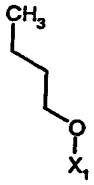
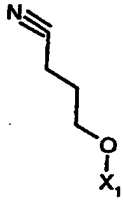
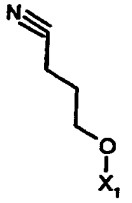
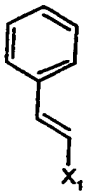
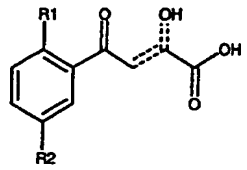
Ex. No.	R1	R2	IC 50 (μM)
51			1.9
52			10
53			0.115
54			2.3
55			10.8

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



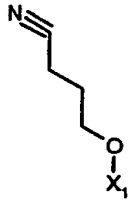
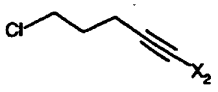
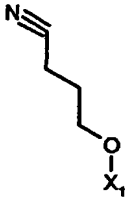
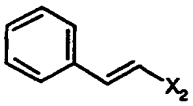
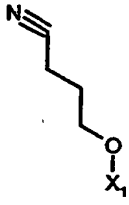
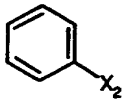
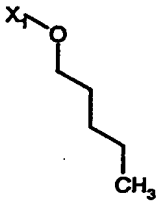
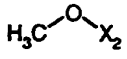
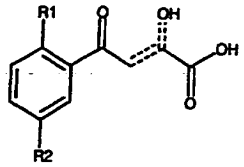
Ex. No.	R1	R2	IC 50 (μM)
56			23.6
57			2.1
58			13.6
59			25.3
60			40

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



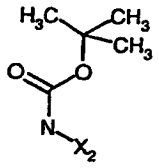
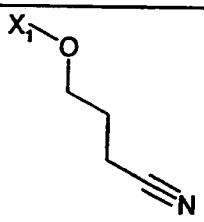
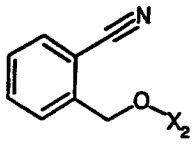
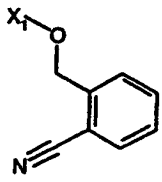
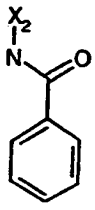
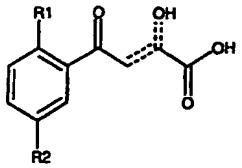
Ex. No.	R1	R2	IC 50 (μM)
61			31
62			10
63			1.7
64			0.23
65			45
66			11

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



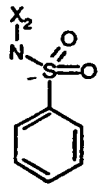
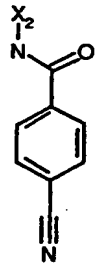
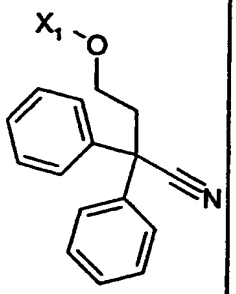
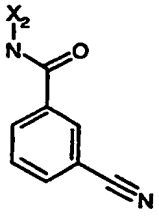
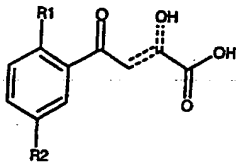
Ex. No.	R1	R2	IC 50 (μM)
67			16
68			30
69			14
70			9.2

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



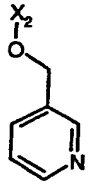
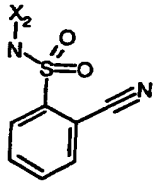
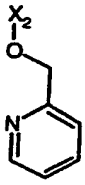
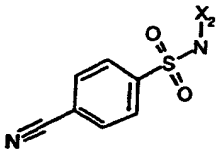
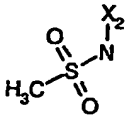
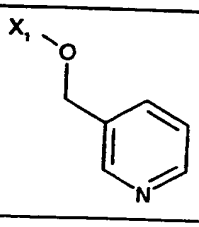
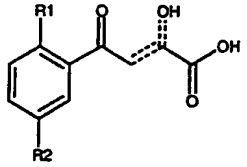
Ex. No.	R1	R2	IC 50 (μM)
71			10.6
72			0.48
73			5.6
74			3.6
75			19.2
76			50

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



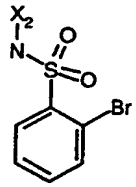
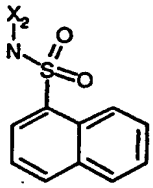
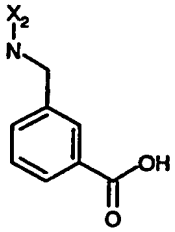
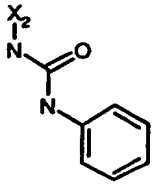
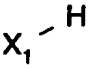
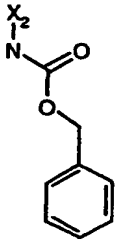
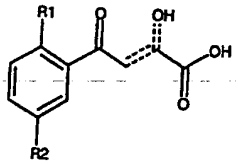
Ex. No.	R1	R2	IC 50 (μM)
77			4.8
78			0.67
79			6
80			3
81			1.4

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



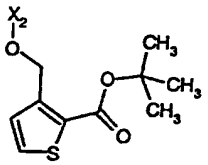
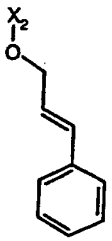
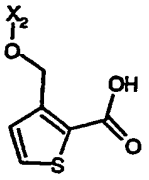
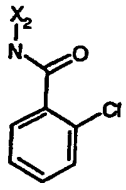
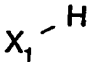
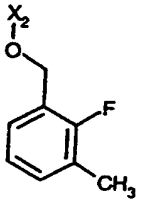
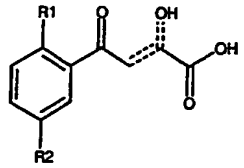
Ex. No.	R1	R2	IC 50 (μM)
82			19
83			9.4
84			0.95
85			13
86			2.05

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



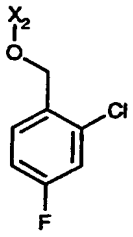
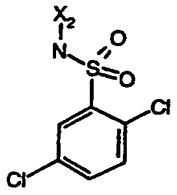
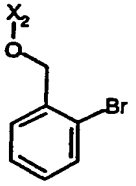
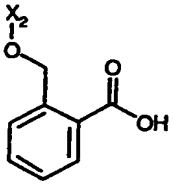
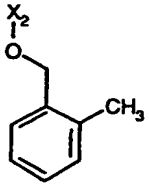
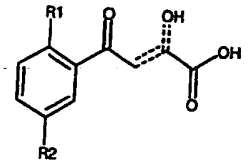
Ex. No.	R1	R2	IC 50 (μM)
87			2.3
88			0.7
89			3.3
90			1.8
91			6.2

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



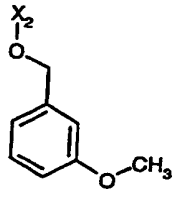
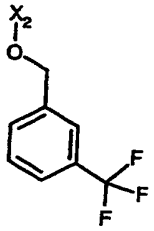
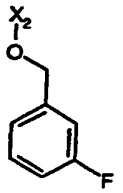
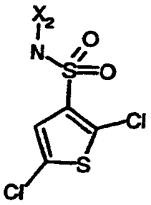
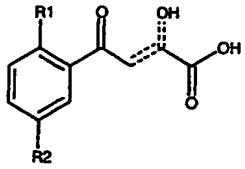
Ex. No.	R1	R2	IC 50 (μM)
92			1
93			1.9
94			5.8
95			0.48

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



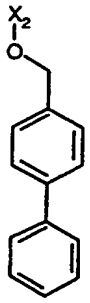
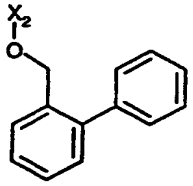
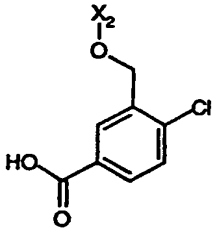
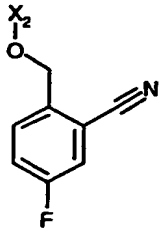
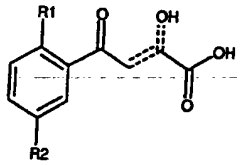
Ex. No.	R1	R2	IC 50 (μM)
96			50
97			2.8
98			1
99			0.6

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



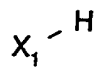
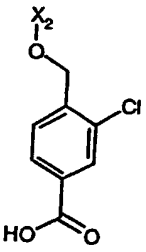
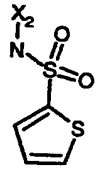
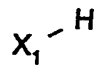
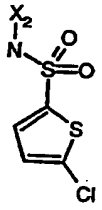
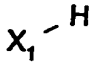
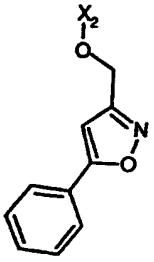
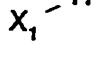
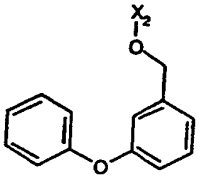
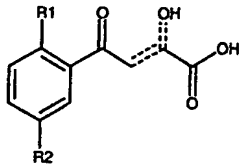
Ex. No.	R1	R2	IC 50 (μM)
100			7.8
101			7
102			1.5
103			6
104			50

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



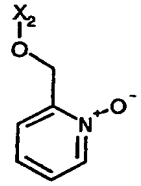
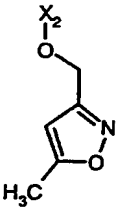
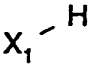
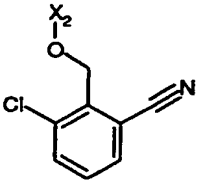
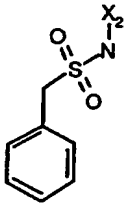
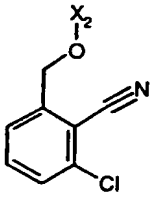
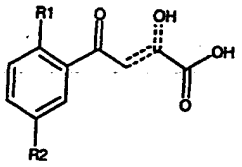
Ex. No.	R1	R2	IC 50 (μM)
105			13.7
106			6.8
107			0.14
108			6.9
109			0.17

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



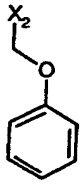
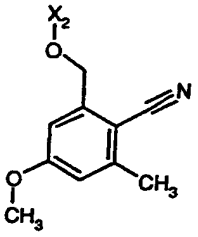
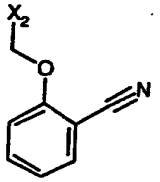
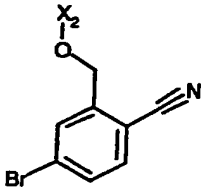
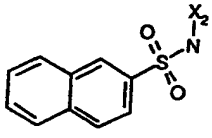
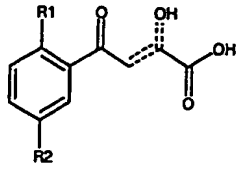
Ex. No.	R1	R2	IC 50 (μM)
110			30
111			0.12
112			1.33
113			0.1
114			0.5

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



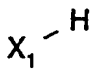
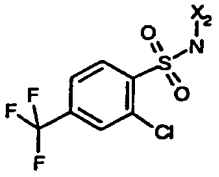
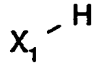
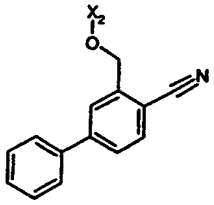
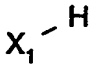
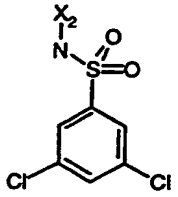
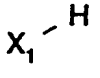
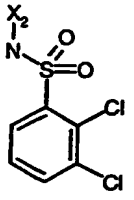
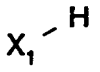
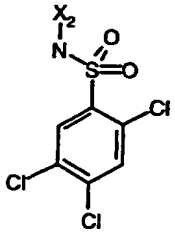
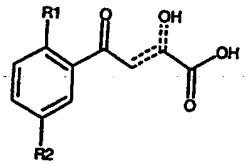
Ex. No.	R1	R2	IC 50 (μM)
115			3.7
116			0.3
117			0.14
118			0.2
119			0.049

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



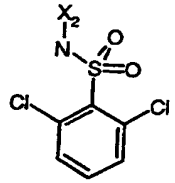
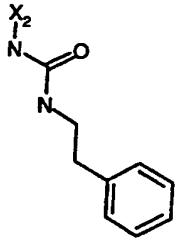
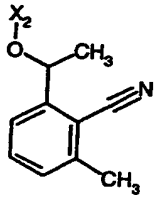
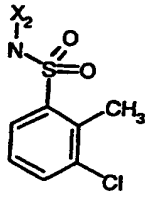
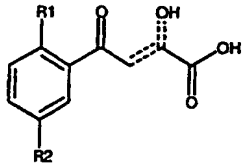
Ex. No.	R1	R2	IC 50 (μM)
120			0.36
121			4
122			2
123			0.29

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



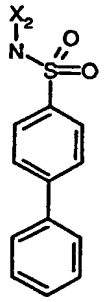
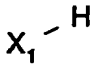
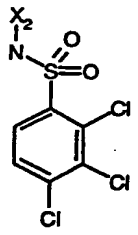
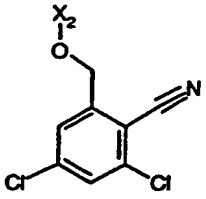
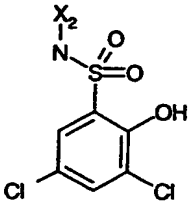
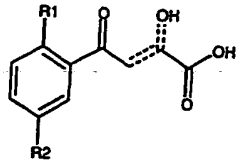
Ex. No.	R1	R2	IC 50 (μM)
124			28
125			0.17
126			0.056
127			0.3

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



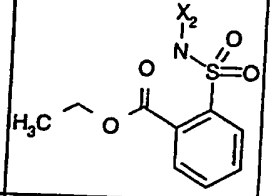
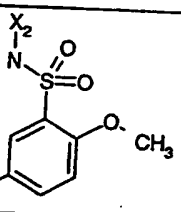
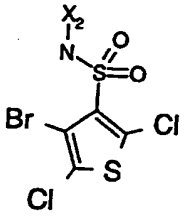
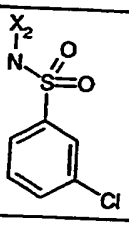
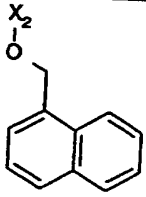
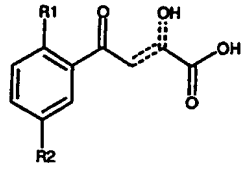
Ex. No.	R1	R2	IC 50 (μM)
128			24
129			1.6
130			0.14
131			0.78
132			0.67

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



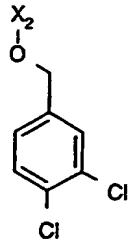
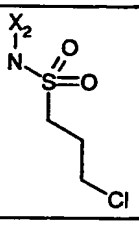
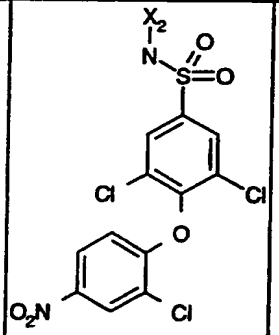
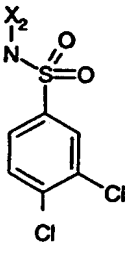
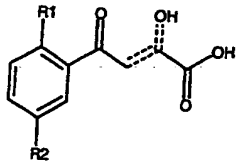
Ex. No.	R1	R2	IC 50 (μM)
133			3.2
134			23
135			21
136			0.2

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



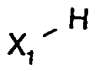
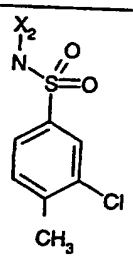
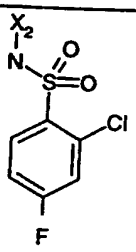
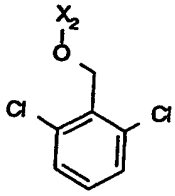
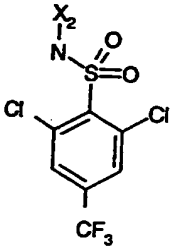
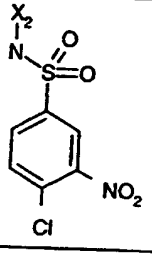
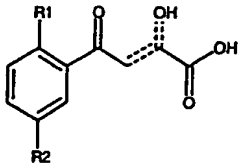
Ex. No.	R1	R2	IC 50 (μM)
137			0.9
138			1.1
139			1.4
140			1
141			0.56

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



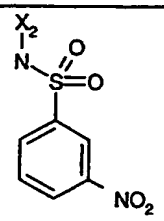
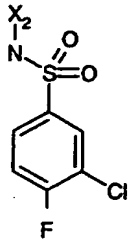
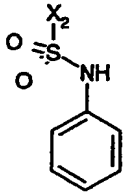
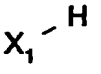
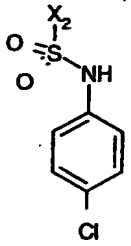
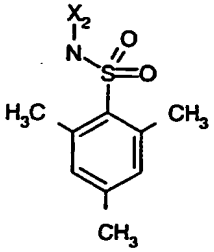
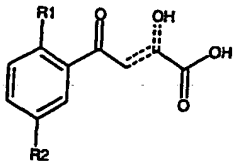
Ex. No.	R1	R2	IC 50 (μM)
142			0.4
143			0.45
144			14
145			1.2
146			15

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



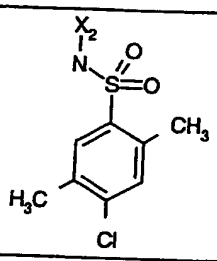
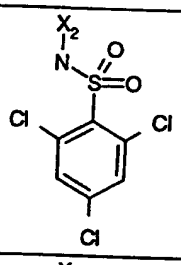
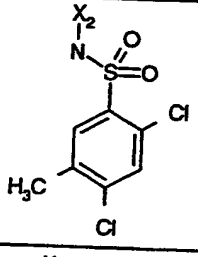
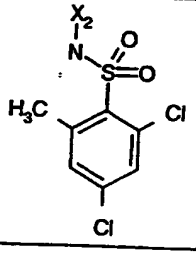
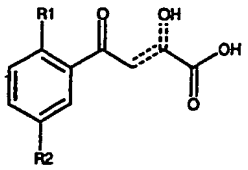
Ex. No.	R1	R2	IC 50 (μM)
147			1.3
148			0.26
149			0.55
150			2.3

Table I

HCV-polymerase inhibitors: examples of 2,5-substituted phenyldiketoacids



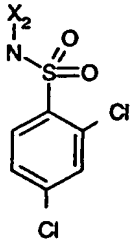
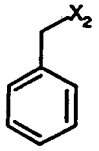
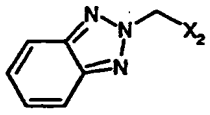
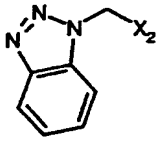
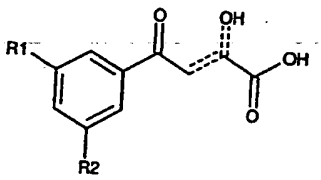
Ex. No.	R1	R2	IC 50 (μM)
151			0.5
152			20
153			19
154			30

Table II

HCV-polymerase inhibitors: examples of 3,5-substituted phenyldiketoacids



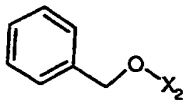
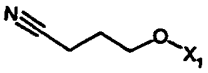
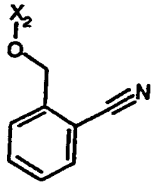
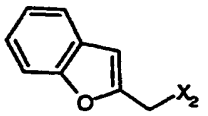
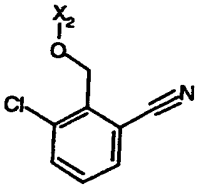
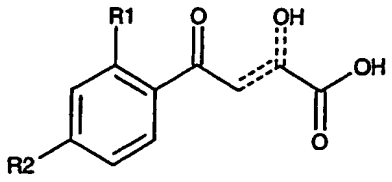
Ex. No.	R1	R2	IC 50 (μM)
155			1.4
156			1.3
157			0.9
158			0.2
159			20
160			0.1

TABLE III

HCV-polymerase inhibitors: examples of 2,4-substituted phenyldiketoacids



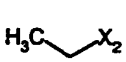
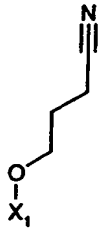
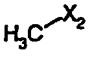
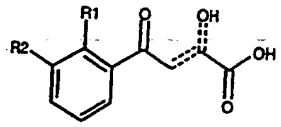
Ex. No.	R1	R2	IC 50 (μM)
161			2.8
162			5.5
163			26
164			47
165			2
166			20
167			0.6

Table IV

HCV-polymerase inhibitors: examples of 2,3-substituted phenyldiketoacids



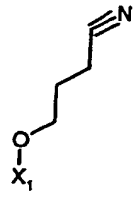
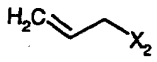
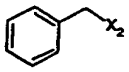
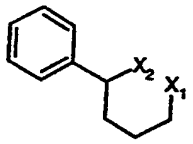
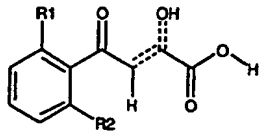
Ex. No.	R1	R2	IC 50 (μM)
168			18
169			>50
170			>50

Table V

HCV-polymerase inhibitors: examples of 2,6-substituted phenyldiketoacids



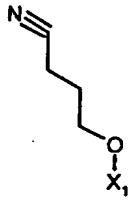
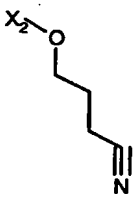
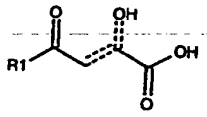
Ex. No.	R1	R2	IC 50 (μM)
171			12
172			>50

Table VIa

HCV-polymerase inhibitors: examples of pyrrole-2-substituted diketoacids



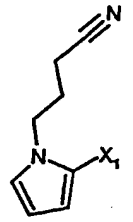
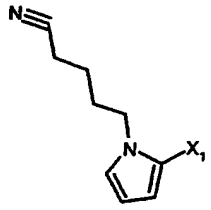
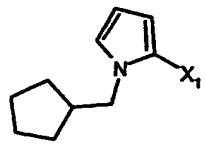
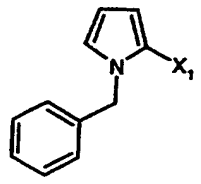
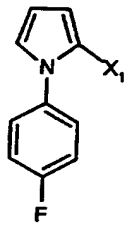
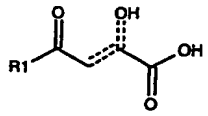
Ex. No.	R1	IC 50 (μM)
173		21
174		13.4
175		25
176		29
177		25

Table VIa

HCV-polymerase inhibitors: examples of pyrrole-2-substituted diketoacids



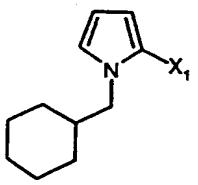
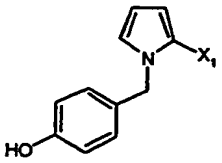
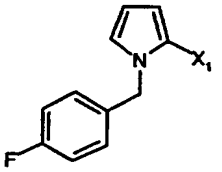
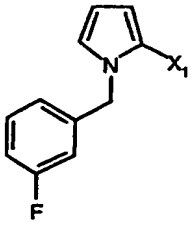
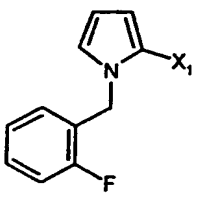
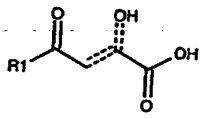
Ex. No.	R1	IC 50 (μM)
178		17.9
179		12.8
180		93
181		30
182		30

Table VIa

HCV-polymerase inhibitors: examples of pyrrole-2-substituted diketoacids



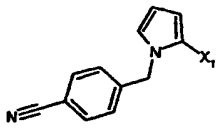
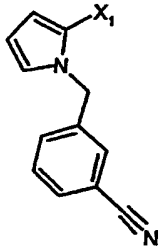
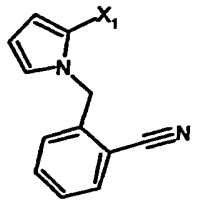
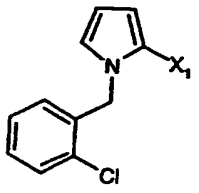
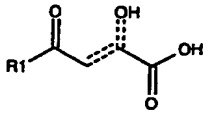
Ex. No.	R1	IC 50 (μM)
183		32
184		6.7
185		6.3
186		24

Table VIa

HCV-polymerase inhibitors: examples of pyrrole-2-substituted diketoacids



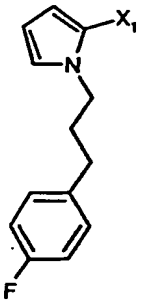
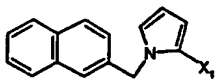
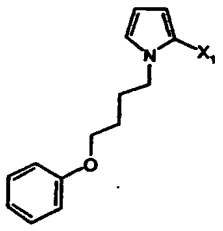
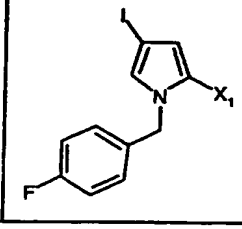
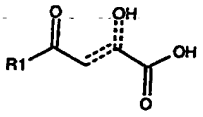
Ex. No.	R1	IC 50 (μM)
187		36
188		12.7
189		28
190		18

Table VIb

HCV-polymerase inhibitors: examples of thiophene-2-substituted diketoacids



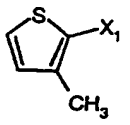
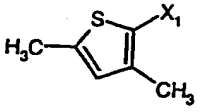
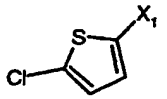
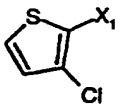
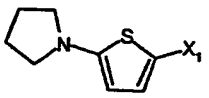
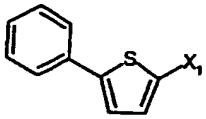
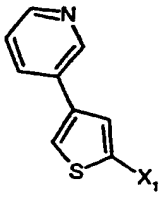
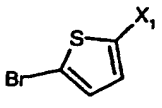
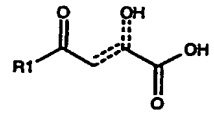
Ex. No.	R1	IC 50 (μM)
191		10
192		8.2
193		12
194		16
195		11.1
196		15
197		11
198		7.9

Table VIb

HCV-polymerase inhibitors: examples of thiophene-2-substituted diketoacids



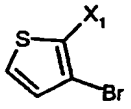
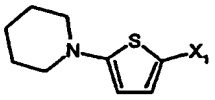
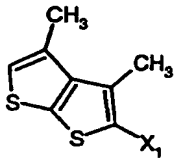
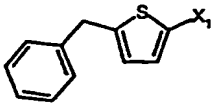
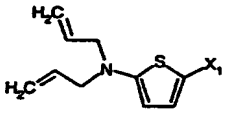
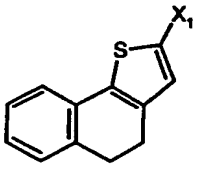
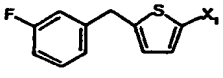
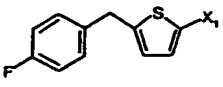
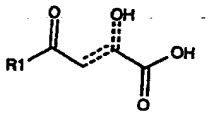
Ex. No.	R1	IC 50 (μM)
199		17
200		8.2
201		20
202		68
203		19.8
204		11
205		74
206		65

Table VIb

HCV-polymerase inhibitors: examples of thiophene-2-substituted diketoacids



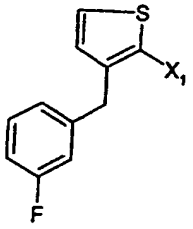
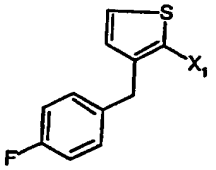
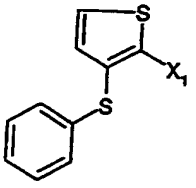
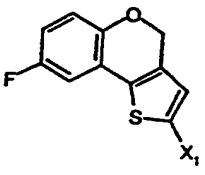
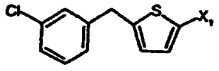
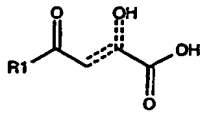
Ex. No.	R1	IC 50 (μM)
207		9.9
208		11.6
209		12.6
210		27
211		82

Table VIb

HCV-polymerase inhibitors: examples of thiophene-2-substituted diketoacids



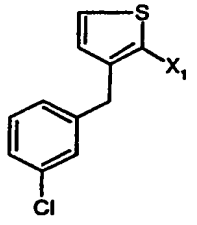
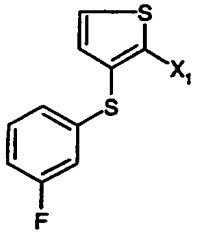
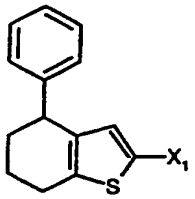
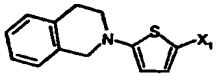
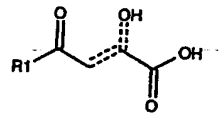
Ex. No.	R1	IC 50 (μM)
212		7.5
213		5.9
214		17
215		15.3

Table VIc

HCV-polymerase inhibitors: examples of furan-2-substituted diketoacids



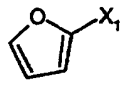
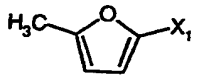
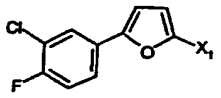
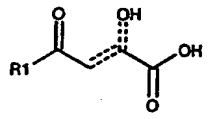
Ex.	R1	IC 50 (μM)
216		50
217		58
218		41.2

Table VIIa

HCV-polymerase inhibitors: examples of pyrrole-3-substituted diketoacids



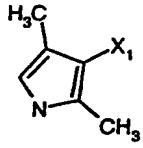
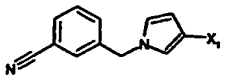
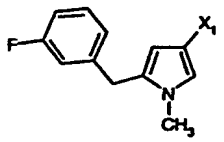
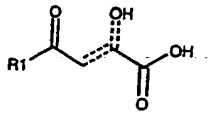
Ex.No.	R1	IC 50 (μM)
219		23.7
220		4.6
221		20.6

Table VIIb

HCV-polymerase inhibitors: examples of thiophene-3-substituted diketoacids



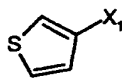
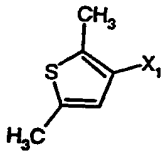
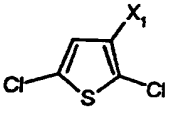
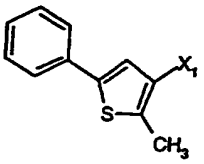
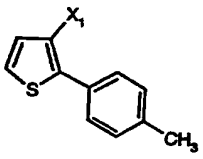
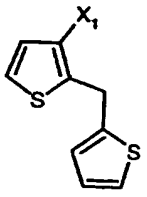
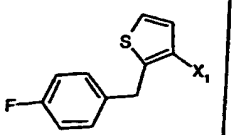
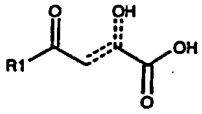
Ex.No.	R1	IC 50 (μM)
222		4
223		27
224		50
225		167
226		17
227		15
228		17.8

Table VIIb

HCV-polymerase inhibitors: examples of thiophene-3-substituted diketoacids



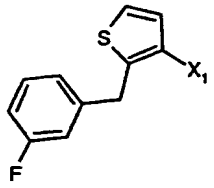
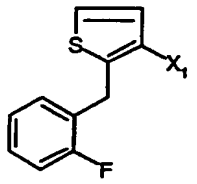
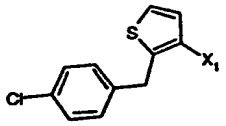
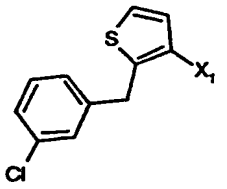
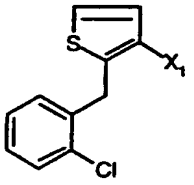
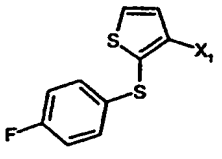
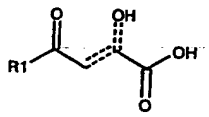
Ex.No.	R1	IC 50 (μM)
229		80
230		8.6
231		9.4
232		11.8
233		9.2
234		14.5

Table VIIb

HCV-polymerase inhibitors: examples of thiophene-3-substituted diketoacids



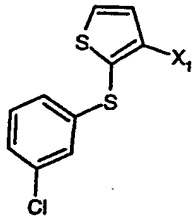
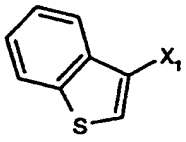
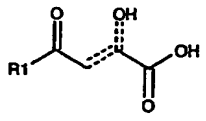
Ex.No.	R1	IC 50 (μM)
235		7.5
236		26

Table VIIc

HCV-polymerase inhibitors: examples of furan-3-substituted diketoacids



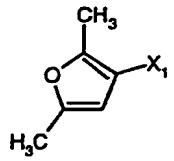
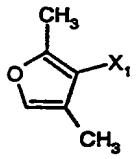
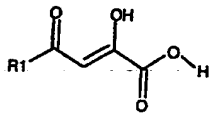
Ex.No.	R1	IC 50 (μM)
237		14
238		47.5

Table VIII

HCV-polymerase inhibitors: examples of alkyl-diketoacids



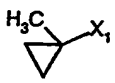
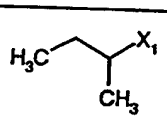
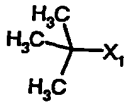
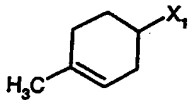
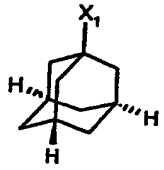
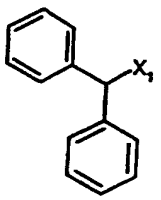
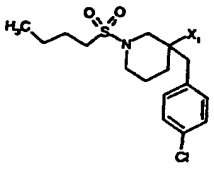
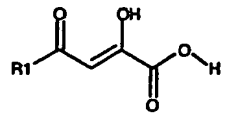
Ex. No.	R1	IC 50 (μM)
239		9.4
240		18
241		37
242		12.8
243		6.7
244		77
245		81.4

Table VIII

HCV-polymerase inhibitors: examples of alkyl-diketoacids



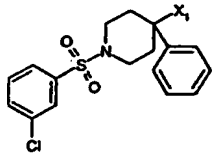
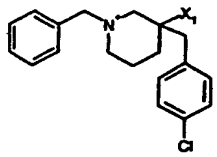
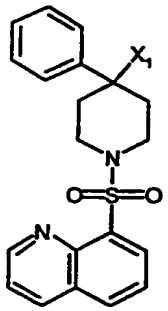
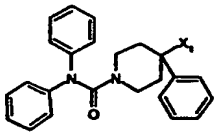
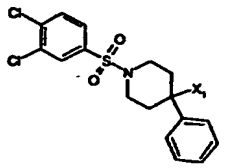
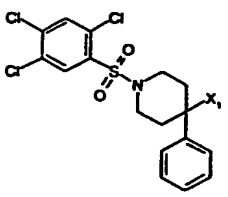
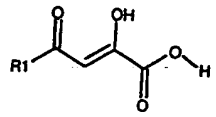
Ex. No.	R1	IC 50 (μM)
246		18
247		45
248		10
249		60
250		17
251		21

Table VIII

HCV-polymerase inhibitors: examples of alkyl- diketoacids



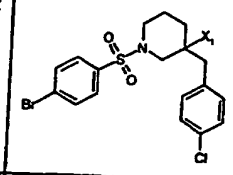
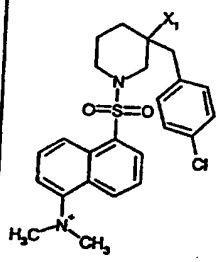
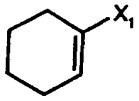
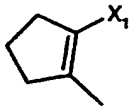
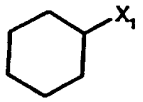
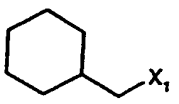
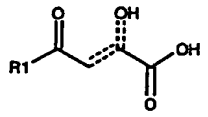
Ex. No.	R1	IC 50 (μM)
252		61
253		55
254		14
255		16.7
256		25
257		50

Table IXa
most active HCV-inhibitors



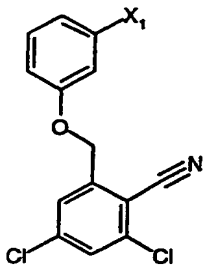
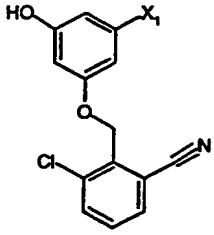
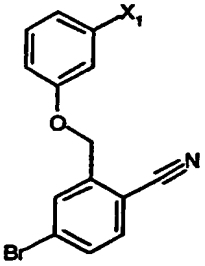
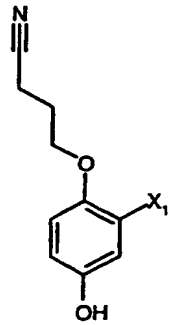
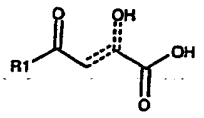
Ex. No.	R1	HCV	HIV	HBV
126		0.056	100	ND
160		0.1	NA	ND
113		0.1	90	ND
53		0.115	37	ND

Table IXa
most active HCV-inhibitors



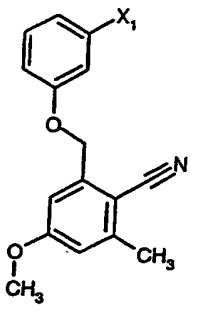
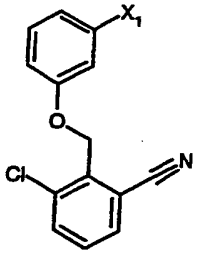
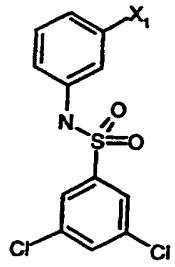
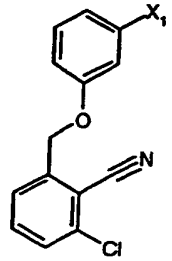
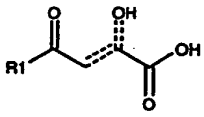
Ex. No.	R1	HCV	HIV	HBV
111		0.12	80	ND
107		0.14	58	ND
117		0.14	100	ND
109		0.17	NA	ND

Table IXa
most active HCV-inhibitors



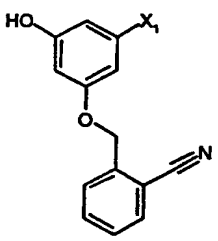
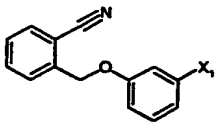
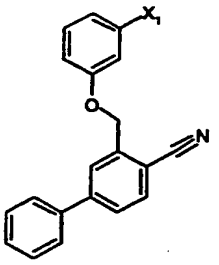
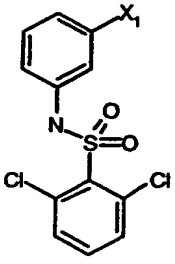
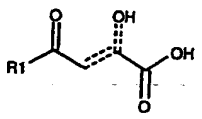
Ex. No.	R1	HCV	HIV	HBV
158		0.2	NA	ND
64		0.23	NA	ND
116		0.3	NA	ND
120		0.36	80	ND

Table IXa
most active HCV-inhibitors



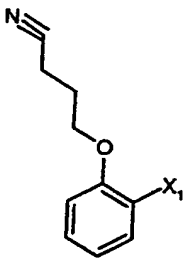
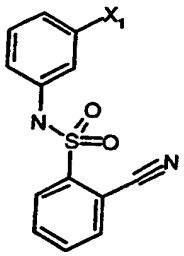
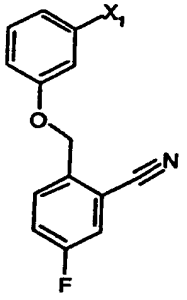
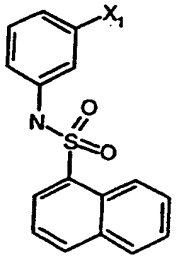
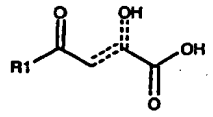
Ex. No.	R1	HCV	HIV	HBV
20		0.38	27	ND
72		0.48	NA	ND
99		0.6	50	ND
78		0.67	35	ND

Table IXa
most active HCV-inhibitors



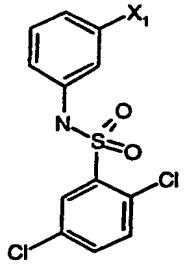
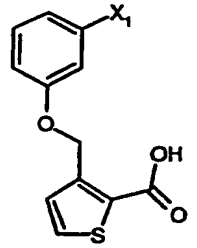
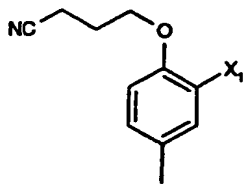
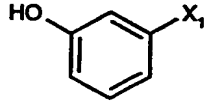
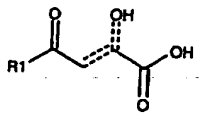
Ex. No.	R1	HCV	HIV	HBV
88		0.7	NA	ND
84		0.95	NA	ND
21		1	>50	ND
23		1	59	ND

Table IXa
most active HCV-inhibitors



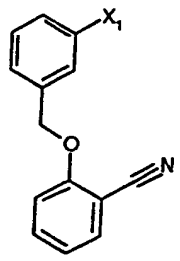
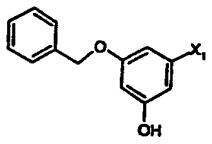
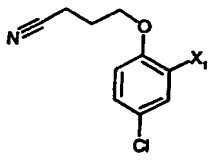
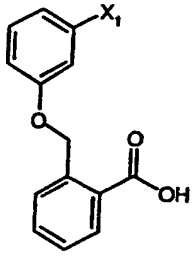
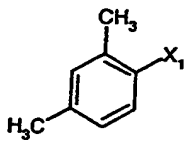
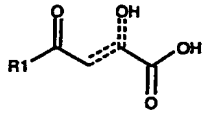
Ex. No.	R1	HCV	HIV	HBV
112		1.33	90	ND
155		1.4	130	416
36		1.6	24	ND
90		1.8	NA	ND
165		2	NA	ND

Table IXa
most active HCV-inhibitors



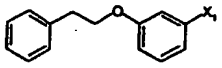
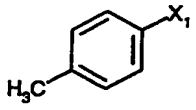
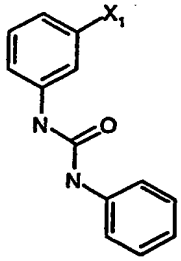
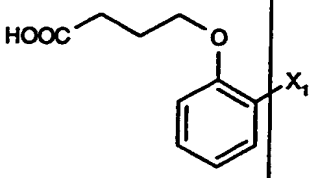
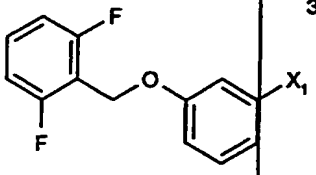
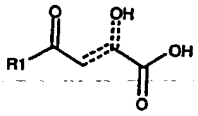
Ex. No.	R1	HCV	HIV	HBV
18		2.2	30	ND
161		2.8	320	108
80		3	NA	ND
27		3	>50	ND
7		3.3	61	6

Table IXa
most active HCV-inhibitors



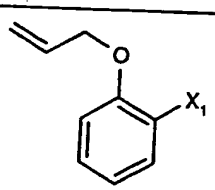
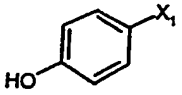
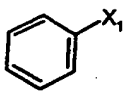
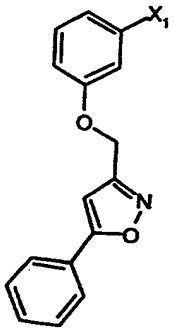
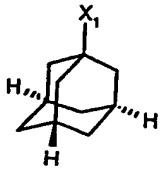
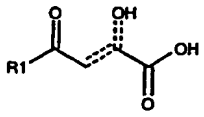
Ex. No.	R1	HCV	HIV	HBV
16		4.3	>100	ND
162		5.5	NA	ND
1		5.6	90	NA
103		6	NA	ND
243		6.7	26.8	ND

Table IXa
most active HCV-inhibitors



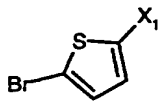
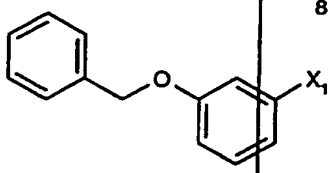
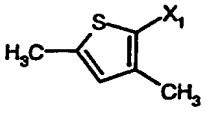
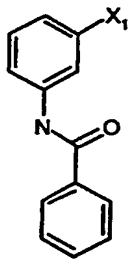
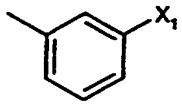
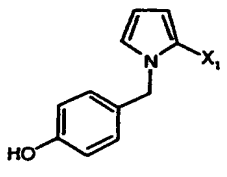
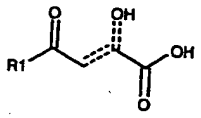
Ex. No.	R1	HCV	HIV	HBV
198		7.9	NA	ND
4		8	>100	ND
192		8.2	NA	ND
66		11	NA	ND
19		12	77	ND
179		12.8	NA	NA

Table IXa

most active HCV-inhibitors



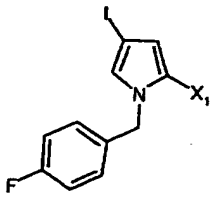
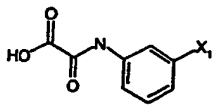
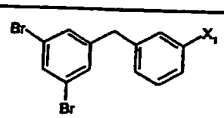
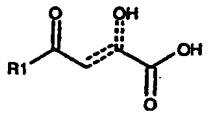
Ex. No.	R1	HCV	HIV	HBV
190		18	NA	NA
24		19	71	ND
49		32	NA	ND

Table IXb
most active HBV-Pol-inhibitors



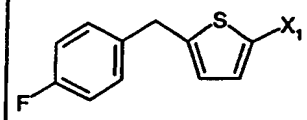
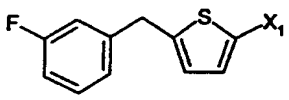
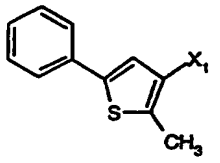
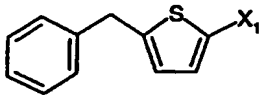
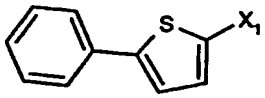
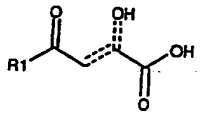
Ex. No.	R1	HCV	HIV	HBV
206		65	NA	2
205		74	NA	3.3
225		167	86	4
202		70	>100	9
196		15	50	9

Table IXc
most active HIV-RT-inhibitors



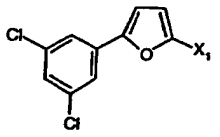
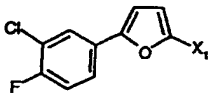
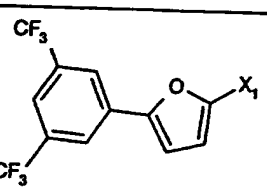
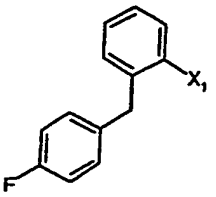
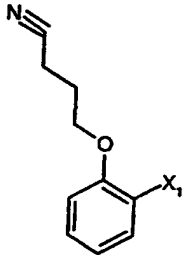
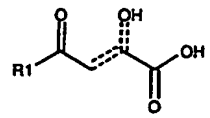
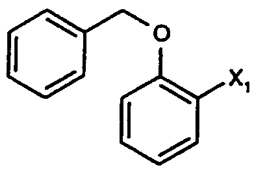
Ex. No.	R1	HCV	HIV	HBV
258		>100	3.6	NA
218		41.2	11.8	40
259		>100	16	NA
40		8.3	12	NA
20		0.38	27	ND

Table IXc
most active HIV-RT-inhibitors



Ex. No.	R1	HCV	HIV	HBV
8		44	19	ND

2. Measurement of Inhibitory Activity

The effectiveness of the compounds set out above as polymerase inhibitors, stated above as IC_{50} values, was assessed in screening assays as follows.

In initial tests, the compounds were tested to see if they were effective as inhibitors of the RNA-dependent RNA polymerase (RdRp) of hepatitis C virus (HCV). The HCV NS5B protein is the viral RdRp; compounds capable of interfering with the activity of this enzyme are thus expected to block viral replication.

Test for Inhibition of Hepatatis C Virus RdRp

WO96/37619 describes the production of recombinant HCV RdRp from insect cells infected with recombinant baculovirus encoding the enzyme. The purified enzyme was shown to possess in vitro RNA polymerase activity using RNA as template. The reference describes a polymerisation assay using poly (A) as a template and oligo(U) as a primer. Incorporation of tritiated UTP is quantified by measuring acid-insoluble radioactivity. The present inventors have employed this assay to screen the various compounds described above as inhibitors of HCV RdRp and other virally encoded polymerases.

Incorporation of radioactive UMP was measured as follows. The standard reaction (100 μl) was carried out in a buffer containing 20mM tris/HCl pH 7.5, 5mM $MgCl_2$, 1mM DTT, 50mM NaCl, 1mM EDTA, 2OU Rnasin (Promega), 0.05% Triton X-100, 1μCi[^{3}H] UTP (40 Ci/mmol, NEN), 10μM UTP and 10 μg/ml poly(A). Oligo $(U)_{12}$ (1μg/ml, Genset) was added as a primer. The final NSSB enzyme concentration was 20 nM. After 1 hour incubation at 22 °C the reaction was stopped by adding 100 μl of 20% TCA and applying samples to DE81 filters. The filters were washed thoroughly with 5% TCA containing 1M Na_2HPO_4/NaH_2PO_4, pH 7.0, rinsed with water and then ethanol, air dried, and the filter-bound radioactivity was measured in the scintillation counter. By carrying out the reaction in the presence of various concentrations of each of the compounds set out above it was possible to determine IC50 values for each compound with the formula:

$$\% \text{ residual activity} = 100/(1+[I]/IC_{50})^s$$

where [I] is the inhibitor concentration and "s" is the slope of the inhibition curve.

Test for Inhibition of Hepatitis B Virus Polymerase

Analogous assays employed the polymerase of hepatitis B virus (HBV pol), obtained in the form of viral particles from the sera of HBV positive patients. These particles

contain a polymerase bound to an incomplete double stranded DNA template. In the assay the incorporation of ^{32}P-dNTP is measured as radioactivity incorporated in acid insoluble precipitate.

The standard reaction (100 µl) was carried out in a buffer containing 50mM tris/HCl pH 7.5, 30mM MgCl 2 , 1mM DTT, 100 mM KCl, 0.02% Triton X-100, 1 µCi[^{32}P] dCTP (300 Ci/mmol, NEN), 1 µM dATP,dTTP, dGTP. After 1 hour incubation at 37 °C the reaction was stopped by adding 100 µl of 20% TCA and applying samples to DE81 filters. The filters were processed and IC_{50} values calculated as described above.

Test for Inhibition of Human Immunodeficiency Virus-1 Reverse Transcriptase

Analogous assays employed the reverse transcriptase of HIV (HIV -1RT) from Boehringer Mannhium.

Incorporation of radioactive dTTP was measured as follows. The standard reaction (100 µl) was carried out in a buffer containing 50mM tris/HCl pH 8.2, 2.5mM MgCl 2, 1mM DTT, 80 mM KCl, 5mM EGTA, 0.05% Triton X-100, 1µCi[3H] dTTP (40 Ci/mmol, NEN), 10 µM UTP and 10 µg/ml poly(A)/dT (from Pharmacia). The final HIV-1RT(enzyme concentration was 1 nM. After 1 hour incubation at 37 °C

the reaction was stopped by adding 100 μl of 20% TCA and applying samples to DE81 filters. The filters were processed and IC_{50} values calculated as described above.

The results demonstrate that the compounds of the present invention are effective as inhibitors of viral polymerases at low micromolar concentrations.

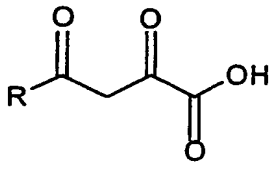
It is apparent from the tables above that a compound of the present invention which is effective in the inhibition of one of the RNA dependent polymerases tested may not necessarily be as effective in inhibiting the other RNA dependent polymerases. The results shown in the tables above indicate a general trend, although this is not without exception. Generally, the most active inhibitors of HCV RdRp contained a phenyl ring attached to the diketoacid, whereas the HIV-RT inhibitors contained a furanyl group and those of HBV polymerase a thiophene group.

While not wishing to be bound by any particular theory, the present inventors hypothesize that the diketoacid fragment of the compounds of the present invention inhibits RNA dependent polymerase activity by providing an "active site anchor" and interacting with divalent

metal cations (Mg^{2+}, Mn^{2+}) required for polymerase activity. The ring system found on the left hand side of the molecule can apparently be modified in order to build specificity towards a given polymerase.

CLAIMS

1. The use of a compound of formula A, or of a pharmaceutically acceptable salt or ester thereof, wherein the group R is an organic moiety containing 2 to 24 carbon atoms which includes an optionally substituted cyclic or heterocyclic group, and wherein one of the atoms in the ring of the cyclic or heterocyclic group is directly bonded to the adjacent carbonyl in the diketoacid, in the manufacture of a medicament for treatment or prophylaxis of a viral illness in a human or animal by inhibition of a viral polymerase.



FORMULA A

2. The use according to claim 1 wherein the medicament is for the inhibition of a DNA polymerase or RNA polymerase.

3. The use according to claim 1 or claim 2 wherein the medicament is for treatment or prevention of infection by an RNA virus, such as a positive single-stranded virus, negative single stranded virus or retrovirus, or a DNA virus.

4. The use according to claim 3 wherein the virus is selected from polio virus, hepatitis C virus, encephalomyocarditis, orthomyxoviruses, paramyxoviruses, HIV, and hepatitis B.

5. The use according to claim 3 wherein the medicament is for the inhibition of hepatitis C virus RNA dependent RNA polymerase (HCV RdRp), hepatitis B virus polymerase (HBV pol), or reverse transcriptase of human immunodeficiency virus (HIV RT).

6. The use according to any one of the following claims wherein the group R is selected from:

(i) optionally substituted aromatic groups;
(ii) optionally substituted heteroaryl groups;
(iii) optionally substituted cycloalkyl groups;
(iv) optionally substituted cycloalkenyl groups; and
(v) optionally substituted cyclic heteroalkyl

groups.

7. A compound of formula A, as set out in claim 1, or a pharmaceutically acceptable salt or ester thereof, for pharmaceutical use, wherein the group R is selected from:

(i) optionally substituted aromatic groups;

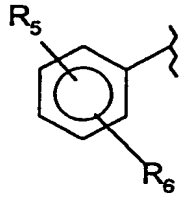
(ii) optionally substituted heteroaryl groups;

(iii) optionally substituted cycloalkyl groups;

(iv) optionally substituted cycloalkenyl groups; and

(v) optionally substituted cyclic heteroalkyl groups, other than those containing a single nitrogen in the ring.

8. A compound, ester or salt according to claim 7 wherein the group R is an optionally substituted phenyl group of formula:



wherein R_5 and R_6 independently are selected from hydrogen and the following substituent groups:

(a) -OH;

(b) -SH;

(c) - halogen, such as fluorine, chlorine or bromine,

(d) - CO_2H;

(e) - CN;

(f) - NO_2 ;

(g) - NR_1R_2 wherein each of R_1 and R_2 is selected from H and lower alkyl groups having 1 to 6 carbon atoms; or R_1 and R_2 together form a ring including 4 to 6 carbon atoms;

(h) - $SO_2NR_1R_2$ where R_1 and R_2 are as defined above;

(i) $-CONR_1R_2$, - NR_1CO_2H, or $-NR_1COCOOH$ where R_1 and R_2 are as defined above;

(j) an alkyl (or alkenyl or alkynyl group) group having 1 to 12 (2 to 12) carbon atoms, preferably 1 to 7 (2 to 7) carbon atoms optionally substituted by any one or more of the groups (a) - (i) above and/or optionally interrupted by a group selected from -O-, -S-, $-NR_3-$,

$-\overset{O}{\overset{\|}{C}}-$, $-CO_2-$, $-OCO-$, $-CONR_3-$, $-NR_3CONR_3-$, $-SO_2-$, $-NR_3SO_2-$, and $-SO_2NR_3-$; where each R_3 independently is H or lower alkyl of 1 to 6 carbon atoms;

(k) an aryl or heteroaryl group having 2 to 10 carbon atoms optionally substituted with any one or more of groups (a) to (j) above;

(l) an aralkyl or heteroaralkyl group having 3 to 16 carbon atoms optionally substituted with any one or more of groups (a) - (j) above and/or in which the alkyl part of the group is optionally interrupted by a group selected from

$-O-$, $-S-$, $-NR_3-$, $-\overset{O}{\overset{\|}{C}}-$ - CO_2-, $-OCO-$, $-CONR_3-$, $-NR_3CONR_3-$, $-SO_2-$, $-NR_3SO_2-$, and - SO_2NR_3- ; where R_3 is as defined above;

(m) $-\overset{O}{\overset{\|}{C}}-R_4$ where R_4 is an alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, or heteroaralkyl group as such groups are defined above at (j), (k) and (l);

(n) $-C(=O)-O-R_4$ or $-O-C(=O)-R_4$ where R_4 is as defined above;

(o) $-OR_4$ where R_4 is as defined above;

(p) $-CNHR_4$, $-NH-C(=O)-R_4$ or $-NH-C(=O)-NHR_4$ where R_4 is as defined above;

(q) $-SO_2R_4$ where R_4 is as defined above;

(r) $-NHR_4$ or $-N(R_4)_2$ where R_4 is as defined above;

(s) $-NHSO_2R_4$ or $-SO_2NHR_4$, where R_4 is as defined above; and

(t) $-SR_4$

and each of optional substituents (j) to (t) above may optionally itself be substituted by one or more groups selected from (j) to (t).

9. A compound, ester or salt according to claim 8 wherein the substituents R_5 and R_6 are independently selected from H-, -OH, $-OR_4$, $-NHSO_2R_4$, lower alkyl, aralkyl, amino, amide, urethane or urea groups.

10. A compound, salt or ester according to claim 8 wherein the substituents R_5 and R_6 are independently selected from H-, -OH, $-OR_4$, and $-NHSO_2R_4$.

11. A compound, salt or ester according to claim 9 or claim 10 containing only one substituent either of formula $-OR_4$ or $-NHSO_2R_4$.

12. A compound, salt or ester of any one of claims 9 to 11 containing a group of formula $-OR_4$ and/or $-NHSO_2R_4$ selected from:

$-OCH_2Ar$;

$-O(CH_2)_2Ar$;

$-O(CH_2)_3CN$;

$-O(CH_2)_3C\equiv CH$; and

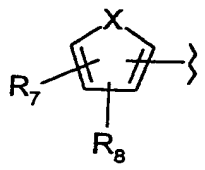
$-NHSO_2Ar$;

wherein Ar is an optionally substituted aryl or heteroaryl group.

13. A compound, salt or ester, according to any one of claims 8 to 12 having a single substituent at a position ortho- or meta- to the diketoacid group.

14. A compound, salt or ester according to any one of claims 8 to 12 having two substituents at the 2,5-; 3,5-; or 2,4-positions.

15. A compound, salt or ester according to claim 7 wherein the group of formula R has the formula:



and each of R_7 and R_8 is independently selected from hydrogen or from the list of substituent groups set out at claim 8, and X is O, S, NH or NR_4, where R_4 is as defined above.

16. A compound, salt or ester according to claim 15 which is a pyrrole-2-substituted diketoacid, a pyrrole-3-substituted diketoacid, a thiophene-2-substituted diketoacid, or a thiophene-3-substituted diketoacid.

17. A compound, salt or ester according to claim 16 which is a pyrrole substituted diketoacid in which each of R_7 and R_8 is hydrogen.

18. A compound, salt or ester according to any one of claims 15 to 17 which is a pyrrole substituted diketoacid having $X=NR_4$ and wherein R_4 is selected

from optionally substituted or interrupted, alkyl aryl or aralkyl groups.

19. A compound, salt or ester according to claim 7 wherein R is selected from cyclopropyl-, cyclopentyl-, cyclohexyl-, cyclopentenyl-, cyclohexenyl and adamantyl groups, any of which may, optionally, be substituted.

20. A pharmaceutical composition comprising a compound, salt or ester of any one of claims 7 to 19 in combination with a pharmaceutically acceptable excipient, diluent or carrier.

21. Use, according to any one of claims 1 to 6, of a compound, salt or ester according to any one of claims 7 to 19.

22. A use according to any one of claims 1 to 6 or 21 wherein the medicament further comprises one or more other agents for the treatment of viral infections.

23. A method of inhibiting a viral polymerase and/or of treating or preventing a viral illness by inhibiting a viral polymerase, the method comprising administering to a human or animal subject suffering

from the condition a therapeutically or prophylactically effective amount of the compound of formula A set out in claim 1, or of a pharmaceutically acceptable salt or ester thereof.

24. A compound of formula A, as set out in claim 1 or a pharmaceutically acceptable salt or ester thereof wherein the group R is selected from:

(i) optionally substituted aromatic groups;

(ii) optionally substituted heteroaryl groups;

(iii) optionally substituted cycloalkyl groups;

(iv) optionally substituted cycloalkenyl groups; and

(v) optionally substituted cyclic heteroalkyl groups, other than those containing a single nitrogen in the ring.

INTERNATIONAL SEARCH REPORT

Inte· ·tional Application No
PCI/GB 99/02446

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C59/76 C07D207/30 C07D307/34 C07D333/04 A61K31/19
A61K31/335 A61K31/40 A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 475 109 A (SELNICK HAROLD G ET AL) 12 December 1995 (1995-12-12) cited in the application table 4	1-6,24
X	TOMASSINI ET AL.: "Inhibition of ...." ANTIMICROB. AGENTS CHEMOTHERAP., vol. 38, no. 12, 1994, pages 2827-2837, XP002119719 table 1	1-14,24
X	DE 32 14 082 A (ROUSSEL UCLAF) 4 November 1982 (1982-11-04) the whole document	7-14,24
X	US 4 337 258 A (ROONEY CLARENCE S ET AL) 29 June 1982 (1982-06-29) claims 1-4	7,24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 1999	10/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Goetz, G

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INTERNATIONAL SEARCH REPORT

Inter 'onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BEILSTEIN INFORMATION SERVICE: FILE: XFIRE, XP002119720 see the compounds attached the whole document	24

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ional Application No
PCT/GB 99/02446

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